

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Quality Control Laboratory

The report is the property of the organization responsible for performing the inspection.

Part 1: General information about the inspection

Name of laboratory	Health Sciences Authority, Applied Sciences Group, Pharmaceutical Division, Pharmaceutical Laboratory, Singapore
Physical address	11 Outram Road Singapore 169078
Postal address	As above
Telephone number	+6562130721
Fax number	+6562130839
Summary of all the activities performed by the manufacturer	The company was involved in: <ul style="list-style-type: none"> • Conventional chemical analysis • Instrumental analysis • Investigation and research
Scope of inspection	Prequalification inspection of QC laboratory
Focus of inspection	<ul style="list-style-type: none"> • Quality system of the Quality Control Laboratory • Conventional chemical analysis • Spectrophotometric analysis (IR, UV) • Chromatographic methods (HPLC, GC, TLC) • Dissolution, disintegration and friability testing
Date of inspection	9 and 10 March, 2009
Programme	Prequalification of Medicines Programme

Part 2: Summary

The Health Sciences Authority, Applied Sciences Group, Pharmaceutical Division, Pharmaceutical Laboratory was inspected on 9 and 10 March 2009.

General information about the Laboratory

Health Sciences Authority (HSA) was formed in April 2001 with the integration of 5 specialized agencies under the Ministry of Health, Singapore, namely Centre for Drug Evaluation, Institute of Science and Forensic Medicine, National Pharmaceutical Administration, Product Regulation Department and Singapore Blood Transfusion Service. Pharmaceutical Laboratory was part of Institute of Science and Forensic Medicine and has been supporting Singapore pharmaceutical regulatory activities for more than 30 years.

In August 2008, the organization was restructured to 3 main professional groups, namely Health Products Regulation Group, Blood Services Group and Applied Sciences Group, to function as consolidated entities comprising Divisions and Branches/Laboratories.

The Pharmaceutical Laboratory in Pharmaceutical Division, under the Applied Sciences Group (ASG) of Health Sciences Authority (HSA), Singapore, serves as a reference chemical quality control laboratory to Singapore's regulatory group which is the Health Product Regulation Group (HPRG) as well as providing analytical services to Government hospitals and clinics.

Applied Sciences Group (ASG) consisted of :

- Forensic Medicine Division
- Forensic Science Division
- Pharmaceutical Division:
 - Pharmaceutical Laboratory
 - Cosmetics Laboratory
 - Cigarettes Testing Laboratory
- Food safety division
- Chemical Metrology Division

The Pharmaceutical Laboratory (hereafter referred to as "Laboratory") employed more than 30 employees.

The Laboratory was collaborating with WHO Centre for Drug Quality Assurance

The Laboratory had the following accreditations:

- Singapore Quality Class Certificate (related to business excellence)
- ASESN Reference Laboratory for Mycotoxins Analysis
- ISO/IEC 17025 - 2006 Accreditation under Singapore Accreditation Council - Singapore Laboratory Accreditation Scheme

The Laboratory did not carry out microbiological tests.

The HSA inspectors delivered 80% of the samples tested by the laboratory, the remaining, 15% were delivered by traders, manufacturers and hospitals and 5 % by the public.

The laboratory did not perform contract analysis for manufacturers. Approximately 3300 samples were analysed per year, including western medicines and traditional (complementary) medicines (the latter comprised quite a large proportion of the total number of samples).

The Laboratory was the leading quality control site in the geographical region for detecting adulterations.

HSA had several MoUs with educational institutions and other authorities in Singapore and in other countries.

Summary of the activities performed by the Laboratory are mentioned in the Table No 1:

Table No 1

Activity	Description
Conventional chemical analysis	The Laboratory is capable of analysing pharmaceutical products based on the following pharmacopoeia:- 1. International Pharmacopoeia (IP) 2. British Pharmacopoeia (BP) 3. United States Pharmacopoeia (USP) 4. European Pharmacopoeia (EP) Accredited test methods as listed in Table No 2.
Instrumental analysis	Analysis performed using Liquid & Gas Chromatography, Mass Spectrometry, Ultra-Violet, FIAS-AAS, ICPMS and various liquid chromatography coupled with mass spectrometry. List of equipment used in the Laboratory is in section 7.1.
Other Analytical Activities	(a) Screening for drug adulteration, toxic alkaloids and heavy toxic metals in traditional medicines (Chinese, ayurvedic etc.) (b) Technical support role in analysing illegal health products.
Investigation and Research	1. Perform investigation on drugs suspected to cause adverse reactions 2. Conduct research on structural elucidation of unknown adulterated compounds in pharmaceutical products and health supplements which include analogues of PDE-5 Inhibitors and other traditional medicines
Other activities	1. Validation of chemical reference substances for ASEAN & WHO 2. Assist WHO in monograph development work 3. Assist traders in pharmaceutical certification and export 4. Provide training to WHO fellows on instrumental analysis of pharmaceutical preparations and good laboratory practice.

The HSA ASG Pharmaceutical Laboratory was accredited for performing the following analysis:

Table No 2.

Type of Analysis	Finished products	Active pharmaceutical Ingredients
Physical / Chemical analysis	pH	pH
	Water content (Karl Fischer)	Water content (Karl Fischer)
	Disintegration time	Acid value
	Tablet hardness	Iodine value
	Density	Melting point
	Dissolution	Clarity & Colour of solutions
	Minimum fill	Acid neutralizing capacity
	Limit Tests	Limit Tests
	Loss on drying	Residue on Evaporation
	Color of solutions	Insoluble matter
	Uniformity of content	Heavy metals (AA and ICPMS)
	Uniformity of weight	Acidity/Alkalinity
		Non volatile matter
		Loss on drying
		Refractive index analysis
Identification	FTIR	FTIR
	TLC	TLC
	HPLC (UV-VIS, PDA, ELSD, FLD)	HPLC (UV-VIS, PDA, ELSD, FLD)
	GC (FID, MS)	GC (FID, MS)
	UV	UV
	CE	CE
	Basic tests	Basic tests
		Optical rotation
Assay, impurities and related substances	HPLC (UV-VIS, PDA, ELSD, FLD)	HPLC (UV-VIS, PDA, ELSD, FLD)
	GC (FID, MS)	GC (FID, MS)
	UV	UV
	FTIR	FTIR
	Volumetric Titrations	Volumetric Titrations
	Determination of related substances and impurities by comparison with a reference standard	Determination of related substances and impurities by comparison with a reference standard
Method Validation	ICH Guidelines	ICH Guidelines

Planned changes:

Launch of Knowledge Enterprise Network (KEN), which links data from different sources (shared M: drive etc).

History of WHO or regulatory agencies inspections

The Laboratory was not previously inspected by the WHO.

Focus of the inspection

This inspection focused on the quality management system of the Laboratory, and analytical activities. The areas of the Good Practices for National Pharmaceutical Quality Control Laboratory guidelines covered in the inspection included the following areas:

- Organization and personnel
- Quality management
- Premises and Equipment
- Documentation
- Sample flow and sample storage
- Reagents and reference substances
- Traceability
- Safety

Detailed summary of the inspection

Day 1 - AM	
OPENING MEETING – 9.00 AM	Introductions
	Objectives and scope of the inspection
	Confirmation of the proposed program
	Recent changes
	Brief presentation of the laboratory
MANAGEMENT AND INFRASTRUCTURE	Quality system
	QM and quality policy
	Organization and management of the labs
	Personnel <ul style="list-style-type: none"> • Organization chart • Job descriptions for key personnel • Training • Work allocation
	Sample receipt
	Reagents storage
	Reagents preparation
	Chemical Laboratory inspection
	Control of reference materials/standards
	Instrumental Laboratory inspection



	<p>Equipment</p> <ul style="list-style-type: none"> • Environment • Operating procedures • Qualification • Calibration • Maintenance • Log books
DAY 2	
Documents review	Documentation system
	Standard operating procedures
	Records including electronic
	Change control
	Customer contracts/agreements
	Complaints
	Documentation system
	Glassware management
	Self inspections
	Evaluation of test results
	Preparation and authorization of C of As
	Method validation
	Electronic systems
	Water system
	General working procedures
Test methods and specifications	
Handling of hazardous material	
Analytical records - raw data, worksheets	
Evaluation of test results	
CLOSING MEETING	

Details to the observations mentioned in the following sections are given in Part 4 of this report.

2.1. ORGANIZATION AND MANAGEMENT

The organization of the Laboratory was defined in an organization chart. The Laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in job role clarifications (job descriptions). The laboratory had a central registry. Records were kept for incoming samples; however see observation regarding isolated cases. The Laboratory had appropriate systems for archiving the documents and handling the samples. Records on samples were kept in electronic form. After the receipt a specific number a 2D barcode was assigned to the sample. The sample number was traceable till the Certificate of Analysis (CoA).

2.2 QUALITY SYSTEM



The Quality system was based on ISO/IEC 17025 standard. Quality assurance documents were approved and available for the Laboratory employees.

ASG had a Quality Manual which consisted of:

- Laboratory Quality manual
- Laboratory Standard Operation Procedures (SOPs)
- Laboratory Manuals
- Other Quality documents

The Quality Service Manager was responsible for maintaining, upgrading and ensuring the quality of service. The Quality Manager was appointed, had direct access to the head of the Laboratory and was assigned to manage the quality assurance program. A Quality Management Committee (QMC) had been formed. On a regular basis the Laboratory carried out Quality Management Meetings (QMM).

The quality system was systematically reviewed by internal audits.

A change control procedure was not available.

The complaint SOP was available; at the time of inspection no complaints had been received by the laboratory.

The validation master plan explaining a validation/qualification approach was not available.

2.3 CONTROL OF DOCUMENTATION

There were procedures in place to generate and approve documents such as SOPs, records and analytical work sheets, as well as procedures for the issuing of certificates of analysis. Distribution of the documents was controlled. Documents were reviewed annually.

2.4 RECORDS

Raw data, calculations and derived data, calibration, validation and verification records and final results were retained. The records included the identity of the personnel involved in sampling, preparation and testing. The records were held secure and in confidence. Test reports on hard copies were kept for 2 years, except for criminal cases where the reports were kept for 5 years.

Quality records included reports from internal audits and management reviews including records from corrective and preventive actions. Internal audit reports were submitted to the accreditation body. Internal audits were carried out annually by ASG QM committee. Corrective actions were proposed by the Laboratory and submitted to the QM meeting for approval. Internal audits were carried out using a check list.

Training records, analytical work sheets and sample logs were available. On spot checks showed that written procedures were available for the performing of the work.



Soft copies of documents were available for all employees on the Share drive. A set of hard copies of authorized SOPs was available in the Laboratory.

A Laboratory Integrated Scientific Administrative Management System (LIMS) was used. The new system LISA (combining StarLIMS and Agilent Open Laboratory Content Management System ECM) had been installed and was used for sample registration, tests assignments, reports generation and dispatch and inventories controls. LISA is standard off-the-shelf software program which had passed the user acceptance testing. Records were available.

2.5 DATA PROCESSING EQUIPMENT

The HPLC systems, GC, UV and IR equipment were linked to the computers operated by their respective software. The related test reports like chromatograms were stored electronically and as hard copies.

2.6 PERSONNEL

An organization chart was showing the arrangements, responsibilities and reporting lines in the Laboratory.

Current job role clarifications were available. Job role clarifications had the following sections:

- Key result areas (KRA). KRA were assessed annually.
- Major activities
- Outcome
- Major challenges
- Key decisions/dimensions
- Skills and knowledge:
 - Education qualifications
 - Relevant experience
 - Personal characteristics & behaviors

A training program for the new recruits was in place. Initial training lasted from 1 to 3 months. Training effectiveness was assessed. An annual schedule for proficiency testing was available for 2009. Training files were maintained for the staff. Reviewed training file was considered to be comprehensive.

2.7 PREMISES

The Laboratory was of a suitable size, the design provided an adequate degree of separation of the activities. The Laboratory had a sufficient number of rooms to isolate different test systems and instruments. The Laboratory had suitable testing equipment available.

In general the storage conditions were acceptable.

A separate archive room was provided for the storage and retrieval of documents. Access to the archive was restricted to designated personnel.

Separate rooms and HPLC equipment were provided for majority of tests performed for detecting adulterations.

2.8 EQUIPMENT, INSTRUMENTS AND OTHER DEVICES

Equipment and instruments were generally designed, located, calibrated, and maintained to suit the operations to be carried out.

Operation and calibration SOPs were available for all equipment. A calibration and preventive maintenance schedule was available.

The list of Laboratory equipment was available.

Some equipment e.g. UVS and dissolution apparatus did not have log books reflecting their use.

2.9 SPECIFICATION ARCHIVE

The specifications were provided by the clients or retrieved from relevant Pharmacopoeias. The specifications were archived together with test reports. The laboratory employees followed confidentiality principles.

2.10 REAGENTS

Purchase of reagents was announced on the web page and any vendor of reagents could apply for the tender in accordance with the governmental procedures.

The preparation of reagents was performed according to the Pharmacopoeia methods. Volumetric solutions were standardized according to the relevant Pharmacopoeia methods.

Expiry dates for liquid reagents was assigned as 6 months, for titration indicators 3 years, for dry reagents 10 years.

Certificates of analysis were not available for the purchased reagents. The inventory of the reagents was available. Smaller amounts of reagents were stored in the Laboratory, larger quantities of procured reagents were stored under contract in another undertaking.

Necessary storage conditions were provided. Flammable substances were stored appropriately.

Water of appropriate quality was used for the chemical and instrumental analysis.

The duty for storekeeping was not defined in the job role clarification of the responsible person.

2.11 REFERENCE MATERIALS



In general, primary drug reference substances were used for qualitative and quantitative tests in pharmacopeia analysis. Secondary drug reference substances were used for screening for western adulterants in complimentary medicines.

For Chinese products the reference herbal material were mostly provided by the Chinese authority.

2.12 CALIBRATION, VALIDATION AND VERIFICATION OF THE EQUIPMENT, INSTRUMENTS AND OTHER DEVICES

Equipment items were uniquely identified. Equipment was calibrated according to the calibration schedule. Labels indicating equipment calibration status (of calibration and due day) were affixed to all equipment and instruments.

Analytical balances were verified daily with standard weights before these were used.

Equipment maintenance was recorded.

2.13 TRACEABILITY

Traceability was assured.

2.14 INCOMING SAMPLES

Incoming samples and corresponding documents were registered in the electronic database. A unique registration number was allocated to the samples and was traceable through all the operations. Incoming samples were allocated to the designated laboratory staff.

A test request was usually drawn by the HSA regulatory group.

The amount of samples was sufficient for analysis and archiving.

2.15 ANALYTICAL WORKSHEET

The analytical worksheets were signed and dated by the laboratory officer, then checked and signed by the scientific officer in charge. Worksheets included required information.

2.16 TESTING

Values obtained from the tests were entered on the analytical worksheets and graphical data were attached. System suitability criteria were fulfilled as defined in the method.

2.17 EVALUATION OF TEST RESULTS

Analytical worksheets were checked by the scientific officer in charge. Test results were subsequently transferred to the STARLIMS by the laboratory officer. Data in the STARLIMS was checked by the scientific officer. Test report was generated by the STARLIMS and approved by the scientific officer. Hard copy of test report was signed by the scientific officer. Test reports in general included the required data.



The SOP dealing with OOS was available for inspection. OOS results were investigated accordingly. There was no separate OOS register. OOS incidents were difficult to retrieve.

2.18 RETAIN SAMPLES

Retain samples were kept for sufficient time period.

2.19 SAFETY

Personnel at the laboratory had to wear protective clothing. Safety instructions were followed. Emergency water showers were provided.

Part 3: Conclusion

The Health Sciences Authority, Applied Sciences Group, Pharmaceutical Division, Pharmaceutical Laboratory, 11 Outram Road 169078 Singapore, was considered to be operating at an acceptable level of compliance with WHO Good practices for national pharmaceutical control laboratories.

All the non-compliances observed during the inspection, that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.